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(54) Title: COMPOSITION FOR TREATING PAIN

(57) Abstract

The present invention provides a composition useful for the treatment of pain, wherein the composition comprises Compound (I) and a Synergistic Analgesic.

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Title

COMPOSITION FOR TREATING PAIN

Field of the Invention

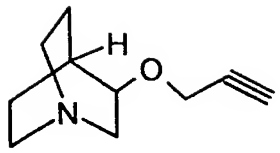
The present invention relates to a method for treating pain using quinuclidine compounds.

Background of the Invention

The method of this invention provides a method for treating pain using a compound which was previously disclosed for use in the treatment of "Alzheimer's Disease, semiole dimentia and cognitive disturbances... be employed for improving memory performance... for peripheral use, e.g. for glaucoma treatment." The method of this invention provides the clinician with another treatment option for the treatment of pain. The compounds used in the presently claimed method appear to have an acceptable side effect profile while providing surprising analgesic activity. The presently claimed composition can provide a synergistic effect for the treatment of pain.

Summary of the Invention

The present invention provides a composition for the treatment of pain comprising a Compound I:



I

or

a pharmaceutically acceptable salt or solvate thereof; and one or more Synergistic Analgesics in a weight ratio of Compound I to Synergistic Analgesic of from about one part Compound I to from about one (1) to about one thousand (1000) parts Synergistic Analgesic.

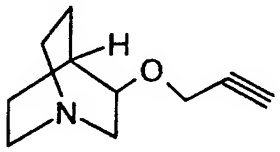
A preferred composition is a weight ratio of Compound I to Synergistic Analgesic of from about one (1) part Compound I to from about one (1) to about one hundred (100) parts Synergistic Analgesic. An especially preferred ratio is from about one part Compound I (1) to from about one (1) to about thirty (30) parts Synergistic Analgesic. A further preferred ratio may be from about one part Compound I to from about one (1) to about ten (10) parts Synergistic Analgesic. A final preferred ratio may be from about one (1) part Compound I to from about one (1) to about three (3) parts Synergistic Analgesic.

One preferred group of Drugs Useful in the Treatment of Pain are Non-Steroidal Antiinflammatory Agents (hereinafter "NSAIDS") and include, but are in no way limited to salicylates such as aspirin. Another preferred group of NSAIDS include, but are not limited to, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, ketoprofen, piroxicam, flurbiprofen, and diclofenac.

Particularly preferred NSAIDS are selected from the group consisting of ibuprofen, and naproxen. Another particularly preferred NSAIDS is aspirin.

The invention further provides a composition for treating pain comprising Compound I or a pharmaceutically acceptable salt or solvate thereof and one or more Synergistic Analgesic in a weight ratio of Compound I to Synergistic Analgesic of from about one part Compound I to from about one (1) to about one thousand (1000) parts Synergistic Analgesic.

The present invention provides a method for treating pain comprising administering to a patient in need thereof, an analgesic composition comprising a Compound I:



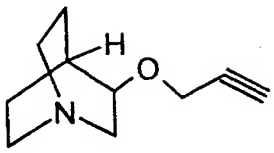
I

or a pharmaceutically acceptable salt or solvate thereof; and

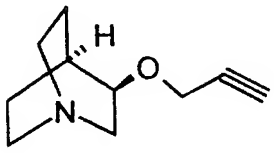
one or more Synergistic Analgesics in a weight ratio of Compound I to Synergistic Analgesic of from about one part Compound I to from about one (1) to about one thousand (1000) parts Synergistic Analgesic.

Detailed Description of the Invention

As noted hereinbefore, the quinuclidine compound referred to herein as Compound I, employed in the method of the present invention is known. The compound, methods of preparing the compounds, as well as pharmaceutical formulations containing the compounds, are disclosed in issued United States Patent number 5,286,864 issued on February 15, 1994, herein incorporated by reference in its entirety. Thus, the artisan can readily prepare the Compound I materials described herein using the teachings in the published patent applications. To further clarify, Compound I shall refer to a compound of the structure:



or
a pharmaceutically acceptable salt or solvate thereof. A particularly preferred Compound I is of the formula II:



II

An especially preferred compound is known as WAL 2014.

As used herein, the term "Synergistic Analgesic" shall mean a compound; or a pharmaceutically acceptable salt thereof, that is known to the artisan to have clinical analgesic activity. As used herein, Synergistic Analgesic shall include, but is in no way limited to, NSAIDS, opioid compounds, and alpha adrenergic compounds.

Drugs Useful in the Treatment of Pain shall also encompass classical analgesic agents known to the artisan. See for example, Goodman and Gillman, The Pharmacological Basis of Therapeutics, 5th edition, Macmillan Publishing Co., 1975, pp 325-358, and similar references commonly consulted by the skilled artisan. Thus, the term shall include, for example, Tylenol #3, tricyclic antidepressants (for example desipramine, imipramine, amytriptiline, nortriptiline), anticonvulsants (for example, carbamazepine, gatapentine, valproate), and serotonin reuptake inhibitors (for example, fluoxetine, paroxetine, citalopram, sertraline), mixed serotonin-norepinephrine reuptake inhibitors (for

example venlafaxine, duloxetine), serotonin receptor agonists and antagonists, cholinergic (muscarinic and nicotinic) analgesics, and neurokinin antagonists.

Especially preferred Drugs Useful in the Treatment of Pain can be selected from the group consisting of tricyclic antidepressants, anticonvulsants, and serotonin-norepinephrine reuptake inhibitors.

The term "alpha-adrenergic compounds", as used herein, represents a compound having central alpha-adrenergic receptor activity. The most preferred central alpha-adrenergic active compound is clonidine or a pharmaceutically acceptable salt thereof having the chemical name: 2-(2,6-dichlorophenylamino)-2-imidazoline. New alpha adrenergic active agents are undergoing pharmacolgoical development. The present invention encompasses all such agents which function as a central alpha-adrenergic active compound.

Clonidine is known to be useful for treating hypertension. *see* Physicians' Desk Reference, 45th Ed. (1991) p. 673.

The term "opioids" or "opioid compounds", as used herein, has the meaning commonly associated with the term by the skilled artisan. Preferred opioid compounds are selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, pentazocine, butorphanol, nabuphine, and buprenorphine.

The term "NSAIDS", as used herein, represents a nonsteroidal anti-inflammatory drug which can be identified as such by the skilled artisan. For example, the Merck Manual, 16th Edition, Merck Research Laboratories (1990) pp 1308 - 1309 provide well known examples of NSAIDS. The term

is intended to include, but is not limited to salicylates such as aspirin. Further, the term includes, but is not limited to, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, ketoprofen, piroxicam, flurbiprofen, and diclofenac. Especially preferred NSAIDS include ibuprofen, and naproxen. Another especially preferred NSAID is aspirin. Particularly preferred NSAIDS include aspirin and ibuprofen. The salicylates may include acetylsalicylic acid, sodium acetylsalicylic acid, calcium acetylsalicylic acid, salicylic acid, and sodium salicylate. The term NSAIDS shall refer to any compound acting as a non-steroidal antiinflammatory agent. Applicants appreciate that new NSAIDS may be in development, and the present invention contemplates a synergistic composition comprising such new agents with Compound I as well.

As used herein, the term "animal" shall refer to a vertebrate animal. Most preferably, the vertebrate animal is a mammal. As used herein, the term "mammal" shall refer to the Mammalia class of higher vertebrates. The term "mammal" includes, but is not limited to, a human. The term "treating" as used herein includes prophylaxis of the named condition or amelioration or elimination of the condition once it has been established.

The term "analgesic dose", as used herein, represents an amount of compound necessary to prevent or treat a human susceptible to or suffering from pain following administration to such human. The active compounds are effective over a wide dosage range. For example, dosages per day will normally fall within the range of about 0.005 to about 500 mg/kg of body weight. In the treatment of adult humans, the range of about 0.05 to about 100 mg/kg, in single or divided doses, is preferred.

However, it will be understood that the amount of the composition actually administered will be determined by

a physician, in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. While the present compounds are preferably administered orally to humans susceptible to or suffering from pain, the compounds may also be administered by a variety of other routes such as the transdermal, parenterally, subcutaneous, intranasal, intramuscular and intravenous routes. Such formulations may be designed to provide delayed or controlled release using formulation techniques which are known in the art.

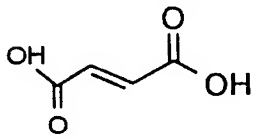
A preferred composition is a weight ratio of Compound I to Synergistic Analgesic of from about one (1) part Compound I to from about one (1) to about one hundred (100) parts Synergistic Analgesic. An especially preferred ratio is from about one part Compound I to from about one (1) to about thirty (30) parts Synergistic Analgesic. A further preferred ratio may be from about one part Compound I to from about one (1) to about ten (10) parts Synergistic Analgesic. A final preferred ratio may be from about one (1) part Compound I to from about one (1) to about three (3) parts Synergistic Analgesic.

As used herein the term "treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed condition once it has been established or alleviation of the characteristic symptoms of such condition.

As used herein the term "pain" shall refer to all types of pain. Preferably, the term shall refer to chronic pains, such as neuropathic pain, and post-operative pain, chronic lower back pain, cluster headaches, herpes

neuralgia, phantom limb pain, central pain, dental pain, neuropathic pain, opioid-resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunburn, post partum pain, migraine, angina pain, and genitourinary tract-related pain including cystitis, the term shall also preferrédly refer to nociceptive pain or nociception.

Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts, and include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, **66**, 2 (1977) which are known to the skilled artisan. An especially preferred salt is



Compositions suitable for internal administration contain from about one half (0.5) milligrams to about 600 milligrams of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of from about 0.5% to about 95% by weight based on the total weight of the composition.

For compositions containing acetaminophen, usually, the daily dosage can be such that the active ingredient is administered at a daily dosage of from about 0.2 mg/kg to about 500 mg/kg of body weight Compound I and from about 0.6 to about 200 mg/kg of acetaminophen.

Typical compositions include Compound I and one or more Synergistic Analgesics, associated with a pharmaceutically acceptable excipient which may be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper, or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

Generally, the compositions of this invention are dispensed in unit form comprising from about 0.1 to about 500 mg in a pharmaceutically acceptable carrier per unit dosage.

The compositions of this invention may be suitable for administration to an animal. Such animals include both domestic animals, for example livestock, laboratory animals, and household pets, and non-domestic animals such as wildlife. More preferably, the animal is a vertebrate. Most preferably, a composition of this invention shall be administered to a mammal. It is especially preferred that the animal is a domestic mammal or a human. For such domestic animal purposes, a composition of this invention may be administered as a feed additive. The most preferred mammal is a human.

The following models and assays are useful for illustrating the effectiveness of the compositions claimed herein.

Nociceptive pain model:

Acetic acid-induced writhing: A standard procedure for detecting and comparing the analgesic activity of different

classes of analgesic drugs for which there is a good correlation with human analgesic activity is the prevention of acetic acid-induced writhing in mice. Mice, are subcutaneously administered various doses of the claimed composition and are injected injected intraperitoneally with acetic acid (0.5% solution, 10 ml/kg) 5 min prior to a designated observation period. For scoring purposes a "writhe" is indicated by whole body stretching or contraction of the abdomen during the observation period beginning 5 min after receiving the acetic acid. Inhibition of writhing behavior is demonstrative of analgesic activity. See, Haubrich, D.R., Ward, S.J., Baizman, E., Bell, M.R., Bradford, J., Ferrari, R., Miller, M., Perrone, M., Pierson, A.K., Saelens, J.K. and Luttinger, D.: Pharmacology of pravadoline: a new analgesic agent. The Journal of Pharmacology and Experimental Therapeutics 255 (1990) 511-522.

Neuropathic pain model:

Sciatic nerve ligation model: Rats are anesthetized and a nerve ligation procedure performed. The common sciatic nerve is exposed and 4 ligatures tied loosely around it with about 1 mm spacing. One day to 10 weeks after surgery, the nociceptive testing is performed. Responses to noxious heat are determined by placing the rats in a chamber with a clear glass floor and aiming at the plantar surface of the affected foot a radiant heat source from beneath the floor. Increased latency to withdraw the hindpaw is demonstrative of analgesic activity. Responses to normally innocuous mechanical stimuli is determined by placing the rats in a chamber with a screen floor and stimulating the plantar surface of the hind paw with graduated von Frey hairs which are calibrated by the grams of force required to bend them. Rats with sciatic nerve ligation respond to lower grams of mechanical stimulation by reflexive withdrawal of the foot than unoperated rats. This response to stimuli which are normally innocuous is termed allodynia. Increases in the

grams of mechanical force required to produce foot withdrawal is demonstrative of antiallodynic activity.

See, Bennett, G.J. and Xie, Y.-K. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 33 (1988) 87-107. See also, Lee, Y.-W., Chaplan, S.R. and Yaksh, T.L.: Systemic and supraspinal, but not spinal, opiates suppress allodynia in a rat neuropathic pain model. Neuroci Lett 186 (1995) 111-114.

Formalin paw test: Rats are anesthetized and when there is a loss of spontaneous movement the rats are injected subcutaneously in the dorsal surface of the hindpaw with 50 ul of 5% formalin solution using a 30 gauge needle. Rats are then individually placed in an open Plexiglas chamber for observation, and within a maximum interval of 1 to 2 min, the animal displays recovery from anesthesia with spontaneous activity and normal motor function. Pain behavior is quantified by periodically counting the incidents of spontaneous flinching/shaking of the injected paw. The flinches are counted for 1-min periods at 1- to 2-, 5- to 6- and 5min intervals during the interval from 10 to 60 min. Inhibition of the pain behavior is demonstrative of an analgesic activity.

See, Malmberg, A.B. and Yaksh, T.L.: Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. The Journal of Pharmacology and Experimental Therapeutics 263 (1992) 136-146.

Inflammatory pain model:

Brewer's yeast-induced hyperalgesia (Randall-Selitto Test): To assess nociceptive threshold in rats, ascending pressure is applied gradually to the paw with a motor driven weight of a Ugo Basile Analgesy Meter. Rats respond to the pressure by either pulling free of the device, struggling or vocalizing. Hyperalgesia is induced by a hind paw subplantar injection of 0.1 ml of 1% suspension of brewer's

yeast in 0.9% saline. The composition of this invention is administered at varying times (0 - 4 hr) after injection of brewer's yeast and pressure threshold for the inflamed paw again determined at varying times. Increases in the pressure which produces a behavioral response is demonstrative of analgesic activity.

See, Haubrich, D.R., Ward, S.J., Baizman, E., Bell, M.R., Bradford, J., Ferrari, R., Miller, M., Perrone, M., Pierson, A.K., Saelens, J.K. and Luttinger, D.: Pharmacology of pravadoline: a new analgesic agent. The Journal of Pharmacology and Experimental Therapeutics 255 (1990) 511-522.

Utility Test Methods

The unexpectedly enhanced analgesic activity of the composition of the invention is evidenced by tests intially conducted on mice. Male mice are fasted for 16-22 hours and weighed. Mice weighing from about 18-22 grams at the time of testing are used for the following studies. All mice are dosed sequentially by the oral route with suspensions of a composition of this invention. Doses are coded using a code unknown to the observer.

A stock suspension of the test composition is prepared by mixing the active ingredients with about 40 mL of an aqueous vehicle containing about 2% Tween 80 (R), a pharmacological dispersant and containing 100% polysorbate 80, and 1% by weight Methocel (R) MC powder, and containing 100% methylcellulose, in distilled water. The mixture may be sonicated for about 10 to about 15 seconds using an ultrasound sytem. All dosing suspensions are prepared by dilution of the stock suspension with Methocel/Tween 80. All suspensions are used within two hours of preparation.

Mouse Writhing Test

An accepted standard for detecting and comparing the analgesic activity of different classes of analgesic compounds for which there is a good correlation with human analgesic activity is the prevention of phenyl-p-benzoquinone induced writhing in mice. [H. Blumberg et al. Proc. Soc. Exp. biol. Med., 118, 763-766 (1965)].

Mice, treated with various doses of Compound I, composition or vehicle are injected intraperitoneally with a standard challenge dose of phenyl-p-benzoquinone 5 minutes prior to a designated observation period. The pheyl-p-benzoquinone is prepared as about 0.1 mg/ml solution in about 5% by volume of ethanol in water. The writhing dose is 1.25 mg/kg injected at a volume of about 0.25ml/10g. For scoring purposes a "writhe" is indicated by whole body stretching or contracting of the abdomen during an observation period beginning about five minutes after the phenyl-p-benzoquinone dose.

All ED50 values and their 95% confidence limits are determined using accepted numerical methods. For example, *see* W.F. Thompson, Bacteriological Rev., **11**, 115-145 (1947). The interaction of the dosages on phenyl-p-benzoquinone induced writhing in mice is demonstrated by the Loewe isobologram (S. Loewe, Pharm. Rev. 9, 237-242 (1957).

The solid line connecting the ED50 dosages of Compound I (alone) and Synergistic Analgesic as claimed herein (alone) represents the "ED50 addition line" which indicates the expected location of the ED50's for Compound I and classical analagesic combinations if simple additivity were to describe their combined effects. The 95% confidence range for the ED50 addition line is shown by the area between the broken lines above and below the ED50 addition line.

According to Loewe's isobolic theory, if the analgesic effects are simply additive to one another, then the expected location of the ED50's of the Compound I and Synergistic Analgesic component of each fixed dosage ratio would be contained within or overlap the region of the ED50 addition line. Combination ED50's located significantly below the ED50 addition line would represent unexpectedly enhanced analgesic activity and combination ED50's located above the line would represent unexpected diminished analgesic effect.

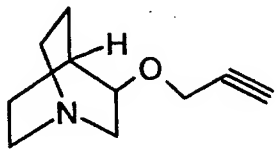
One method to establish the significance of such unexpected enhanced or diminished activity is to calculate the best fitting polynomial regression line to the observed ED50's using standard mathematical techniques.

Such experiments demonstrate that compositions comprised of a Compound I and one or more Synergistic Analgesics provides a statistically significant synergistic analgesic effect.

Preferred Compound I compounds are of Formula II, hereinabove.

We Claim:

1. A composition for treating pain comprising Compound I



I

or

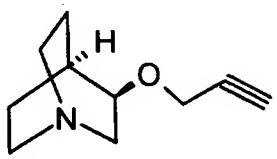
a pharmaceutically acceptable salt or solvate thereof; and one or more Synergistic Analgesic in a weight ratio of from about one part Compound I to from about one (1) part to about one thousand (1000) parts Synergistic Analgesic.

2. A composition of **Claim 1** wherein the weight ratio of Compound I to Synergistic Analgesic is from about one part Compound I to from about one (1) to about one hundred (100) parts Synergistic Analgesic.

3. A composition of **Claim 2** wherein the weight ratio is from about one part Compound I to from about one (1) to about thirty (30) parts Synergistic Analgesic.

4. A composition of **Claim 3** wherein the weight ratio is from about one part Compound I to from about one (1) to about ten (10) parts Synergistic Analgesic.

5. A composition of **Claim 1** wherein Compound I is



II.

6. A composition of **Claim 5** wherein the Synergistic Analgesic is selected from the group consisting of morphine, acetaminophen, ibuprofen, and diclofenac.

7. A composition of **Claim 1** wherein the Synergistic Analgesic is an NSAIDS.

8. A composition of **Claim 7** wherein the NSAIDS is selected from the group consisting of aspirin, indomethacin, ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate, keoprofen, piroxicam, flurbiprofen, and diclofenac or a pharmaceutically acceptable salt thereof.

9. A composition of **Claim 1** wherein the Synergistic Analgesic is an opioid compound.

10. A composition of **Claim 2** wherein the Synergistic Analgesic is an opioid compound.

11. A composition of **Claim 5** wherein the Synergistic Analgesic is an opioid compound.

12. A composition of **Claim 11** wherein the Synergistic Analgesic is an opioid compound is selected from the group consisting of morphine, codeine, meperidine, methadone, propoxyphene, levorphanol, hydromorphone, oxymorphone, oxycodone, brompton's cocktail, pentazocine, butorphanol, nabuphine, and buprenorphine.

13. A composition of **Claim 12** wherein the opioid compound is selected from the group consisting of

morphine, oxymorphine, oxycodone, hydromorphine, codeine, and methadone.

14. A composition of **Claim 1** wherein the Synergistic Analgesic is selected from the group consisting of Tylenol #3, tricyclic antidepressants (for example desipramine, imipramine, amytriptiline, nortriptiline), anticonvulsants (for example, carbamazepine, gatapentine, valproate), and serotonin reuptake inhibitors (for example, fluoxetine, paroxetine, citalopram, sertraline), mixed serotonin-norepinephrine reuptake inhibitors (for example venlafaxine, duloxetine), serotonin receptor agonists and antagonists, cholinergic (muscarinic and nicotinic) analgesics, and neurokinin antagonists.

15. A composition of **Claim 14** wherein the Synergistic Analgesic is selected from the group consisting of Tylenol #3, tricyclic antidepressants, anticonvulsants, and serotonin reuptake inhibitors, mixed serotonin-norepinephrine reuptake inhibitors analgesics, and neurokinin antagonists.

16. A composition of **Claim 15** wherein the Synergistic Analgesic is a tricyclic antidepressant.

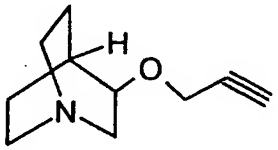
17. A composition of **Claim 1** wherein the Synergistic Analgesic is an alpha adrenergic compound.

18. A composition of **Claim 18** central alpha-adrenergic active compound is Clonidine or a pharmaceutically acceptable salt thereof.

19. A composition of **Claim 1** wherein the composition can provide a synergistic analgesic effect.

20. A composition of **Claim 2** wherein the composition can provide a synergistic analgesic effect.

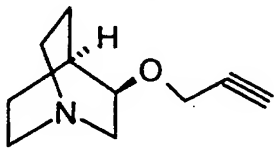
21. A method for treating pain comprising administering an analgesic dose of a composition comprising Compound I



or

a pharmaceutically acceptable salt or solvate thereof; and one or more Synergistic Analgesic in a weight ratio of Compound I to Synergistic Analgesic of from about one part Compound I to from about one (1) to about one thousand (1000) parts Synergistic Analgesic.

22. A method of **Claim 21** wherein Compound I is



II.

23. A method of **Claim 22** wherein the weight ratio of Compound I to Synergistic Analgesic is from about one part Compound I to from about one to about one hundred (100) parts Synergistic Analgesic.

24. A method of **Claim 21** wherein the Synergistic Analgesic is an NSAIDS.

25. A method of **Claim 22** wherein the Synergistic Analgesic is selected from the group consisting of alpha adrenergic compounds and opioid compounds.

26. A method of **Claim 22** wherein the Synergistic Analgesic is selected from the group consisting of Tylenol #3, tricyclic antidepressants, anticonvulsants, and serotonin reuptake inhibitors, mixed serotonin-norepinephrine reuptake inhibitors analgesics, and neurokinin antagonists.

27. A method of **Claim 22** wherein the Synergistic Analgesic is an opioid compound.

28. A method of **Claim 22** wherein pain is neuropathic pain.

29. A method of **Claim 22** wherein pain is nociceptive pain.

30. A method of **Claim 22** wherein the pain is acute pain.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07501

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :CO7D 453/02; A61K 31/46
US CL :514/305; 546/137
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/305; 546/137

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEMICAL ABSTRACTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,286,864 A (WALTHER et al) 15 February 1994, see entire document.	1-30
A	US 5,451,586 A (LOWE, III) 19 September 1995, see entire document.	1-30
A,P	US 5,691,349 A (MALLION et al) 25 November 1997, see entire document.	1-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 18 JUNE 1998	Date of mailing of the international search report 27 July 1998
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